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Atty Dkt. No. 23001481
USSN: 09/297,648

CERTIFICATE OF MAILING			
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Typed or Printed Name	Steven F. Goldstein		
Signature	Steven F. Goldstein	Date	May 29, 2001

DECLARATION OF FILIPPO M. RANDAZZO AND GEORGE F. LAMSON UNDER 37 C.F.R. § 1.132 Address to: Assistant Commissioner for Patents Washington, D.C. 20231	Attorney Docket	23001481
	First Named Inventor	Williams et al.
	Application Number	09/297,648
	Filing Date	March 10, 2000
	Group Art Unit	1631
	Examiner Name	J. Brusca
	Title: *Novel Human Genes and Gene Expression Products II*	

Dear Sir:

1. I, Filippo M. Randazzo, declare and say I am a resident of the State of California. My residence address is 104 Capricorn Avenue, Oakland, CA 94611.

2. I hold a B.S. degree in Molecular Microbiology and Anthropology, which I received from the University of Notre Dame in 1985. I further hold a Ph.D. degree, which I received from Indiana University in 1991. I am skilled in the fields of genetics, molecular biology, developmental biology genomics and cancer biology. I am a co-inventor of the invention claimed in the above-referenced patent application.

3. I, George F. Lamson, declare and say I am a resident of the State of California. My residence address is 232 Sandringham Dr., Moraga, CA 94556.

4. I hold a BS degree in Biochemistry, which I received from the University of CA, Santa Barbara in 1976. I further hold a PhD degree, which I received from University of CA,

Berkeley, in 1982. I am skilled in the fields of Bioinformatics. I am a co-inventor of the invention claimed in the above-referenced patent application.

5. I have reviewed the relevant portions of the Office Action (specifically section nos. 2 and 5), mailed November 29, 2000, in the above-referenced application. I understand that claims 40-66 and 85-102 of the above-referenced patent application are rejected under 35 U.S.C. § 101 on the grounds that the claimed invention lacks patentable utility, and also under 35 U.S.C. § 112, ¶ 1, on the grounds that since the claimed invention is not supported by a patentable utility, one skilled in the art would not know how to use the claimed invention.

6. This Declaration provides further evidence of the patentable utility of the claimed invention. Specifically, this Declaration provides evidence that the nucleotide sequences designated SEQ ID NOS:739, 1899 and 2007 represent genes that are differentially expressed in cancer cells, thus supporting the assertion that the claimed invention has utility in detecting cancer cells.

7. The following experiments were conducted by me or under my direction.

8. Genes differentially expressed in cancerous cells were identified as detected by microarray hybridization analysis using materials obtained from patient colon tissue samples. The biological materials used in these experiments, the methods of analysis, and the results are described below.

9. **Source of patient tissue samples**. Normal and cancerous tissues were collected from patients using laser capture microdissection (LCM) techniques, which techniques are well known in the art. **Table 1** (Attachment 1) provides information about each patient from which the samples were isolated, including: the Patient ID and Path ReportID, numbers assigned to the patient and the pathology reports for identification purposes; the anatomical location of the tumor (AnatomicalLoc); the Primary Tumor Size; the Primary Tumor Grade; the Histopathologic Grade; a description of local sites to which the tumor had invaded (Local

Invasion); the presence of lymph node metastases (Lymph Node Metastasis); incidence of lymph node metastases (provided as number of lymph nodes positive for metastasis over the number of lymph nodes examined) (Incidence Lymphnode Metastasis); the Regional Lymphnode Grade; the identification or detection of metastases to sites distant to the tumor and their location (Distant Met & Loc); a description of the distant metastases (Description Distant Met); the grade of distant metastasis (Distant Met Grade); and general comments about the patient or the tumor (Comments). Adenoma was not described in any of the patients. Adenoma dysplasia (described as hyperplasia by the pathologist) was described in Patient ID No. 695. Extranodal extensions were described in two patients, Patient ID Nos. 784 and 791. Lymphovascular invasion was described in seven patients, Patient ID Nos. 128, 278, 517, 534, 784, 786, and 791. Crohn's-like infiltrates were described in seven patients, Patient ID Nos. 52, 264, 268, 392, 393, 784, and 791.

10. **Source of polynucleotides on arrays.** Polynucleotides spotted on the arrays were generated by PCR amplification of clones derived from cDNA libraries. The clones used for amplification were either the clones from which the sequences described herein were derived, or are clones having inserts with significant polynucleotide sequence overlap with the sequences described herein as determined by BLAST2 homology searching.

11. **Microarray Design**. Each array used in the examples below had an identical spatial layout and control spot set. Each microarray was divided into two areas, each area having an array with, on each half, twelve groupings of 32 x 12 spots for a total of about 9,216 spots on each array. The two areas are spotted identically which provide for at least two duplicates of each clone per array. Spotting was accomplished using PCR amplified products from 0.5kb to 2.0 kb and spotted using a Molecular Dynamics Gen III spotter according to the manufacturer's recommendations. The first row of each of the 24 regions on the array had about 32 control spots, including 4 negative control spots and 8 test polynucleotides. The test polynucleotides were spiked into each sample before the labeling reaction with a range of concentrations from 2-600 pg/slide and ratios of 1:1. For each array design, two slides were hybridized with the test samples reverse-labeled in the labeling reaction. This provided for about 4 duplicate measurements for each clone, two of one color and two of the other, for each sample.

12. **Microarray Analysis.** cDNA probes were prepared from total RNA isolated from the patient cells described in **Table 1** (Attachment 1). Since LCM provides for the isolation of specific cell types to provide a substantially homogenous cell sample, this provided for a similarly pure RNA sample. Total RNA was first reverse transcribed into cDNA using a primer containing a T7 RNA polymerase promoter, followed by second strand DNA synthesis. cDNA was then transcribed *in vitro* to produce antisense RNA using the T7 promoter-mediated expression, and the antisense RNA was then converted into cDNA. The second set of cDNAs were again transcribed i*n vitro*, using the T7 promoter, to provide antisense RNA. Optionally, the RNA was again converted into cDNA, allowing for up to a third round of T7-mediated amplification to produce more antisense RNA. Thus the procedure provided for two or three rounds of *in vitro* transcription to produce the final RNA used for fluorescent labeling. Fluorescent probes were generated by first adding control RNA to the antisense RNA mix, and producing fluorescently labeled cDNA from the RNA starting material. Fluorescently labeled cDNAs prepared from the tumor RNA sample were compared to fluorescently labeled cDNAs prepared from normal cell RNA sample. For example, the cDNA probes from the normal cells were labeled with Cy3 fluorescent dye (green) and the cDNA probes prepared from the tumor cells were labeled with Cy5 fluorescent dye (red).

13. The differential expression assay was performed by mixing equal amounts of probes from tumor cells and normal cells of the same patient. The arrays were prehybridized by incubation for about 2 hrs at 60°C in 5X SSC/0.2% SDS/1 mM EDTA, and then washed three times in water and twice in isopropanol. Following prehybridization of the array, the probe mixture was then hybridized to the array under conditions of high stringency (overnight at 42°C in 50% formamide, 5X SSC, and 0.2% SDS. After hybridization, the array was washed at 55°C three times as follows: 1) first wash in 1X SSC/0.2% SDS; 2) second wash in 0.1X SSC/0.2% SDS; and 3) third wash in 0.1X SSC. The arrays were then scanned for green and red fluorescence using a Molecular Dynamics Generation III dual color laser-scanner/detector. The images were processed using BioDiscovery Autogene software, and the data from each scan set normalized to provide for a ratio of expression relative to normal. Data from the microarray

experiments was analyzed according to the algorithms described in U.S. application serial no. 60/252,358, filed November 20, 2000, by E.J. Moler, M.A. Boyle, and F.M. Randazzo, and entitled "Precision and accuracy in cDNA microarray data." The experiment was repeated, this time labeling the two probes with the opposite color in order to perform the assay in both "color directions." Each experiment was sometimes repeated with two more slides (one in each color direction). The level fluorescence for each sequence on the array expressed as a ratio of the geometric mean of 8 replicate spots/genes from the four arrays or 4 replicate spots/gene from 2 arrays or some other permutation. The data were normalized using the spiked positive controls present in each duplicated area, and the precision of this normalization was included in the final determination of the significance of each differential. The fluorescent intensity of each spot was also compared to the negative controls in each duplicated area to determine which spots detected significant expression levels in each sample.

14. A statistical analysis of the fluorescent intensities was applied to each set of duplicate spots to assess the precision and significance of each differential measurement, resulting in a p-value testing the null hypothesis that there is no differential in the expression level between the tumor and normal samples of each patient. For initial analysis of the microarrays, the hypothesis was accepted if $p>10^{-3}$, and the differential ratio was set to 1.000 for those spots. All other spots have a significant difference in expression between the tumor and normal sample. If the tumor sample has detectable expression and the normal does not, the ratio is truncated at 1000 since the value for expression in the normal sample would be zero, and the ratio would not be a mathematically useful value (e.g., infinity). If the normal sample has detectable expression and the tumor does not, the ratio is truncated to 0.001, since the value for expression in the tumor sample would be zero and the ratio would not be a mathematically useful value. These latter two situations are referred to herein as "on/off." Database tables were populated using a 95% confidence level ($p>0.05$).

15. In general, a polynucleotide is said to represent a significantly differentially expressed gene between two samples when there is detectable levels of expression in at least one sample and the ratio value is greater than at least about 1.2 fold, preferably greater than at least about 1.5

fold, more preferably greater than at least about 2 fold, where the ratio value is calculated using the method described above. A differential expression ratio of 1 indicates that the expression level of the gene in the tumor cell was not statistically different from expression of that gene in normal colon cells of the same patient. A differential expression ratio significantly greater than 1 in cancerous colon cells relative to normal colon cells indicates that the gene is increased in expression in cancerous cells relative to normal cells, indicating that the gene plays a role in the development of the cancerous phenotype, and may be involved in promoting metastasis of the cell.

16. **Table 2**, shown below, summarizes the results of the differential expression analysis in colon tissue. The table provides: the SEQ. ID. NO. of the polynucleotide corresponding to the polynucleotide on the spot on the array; the Sequence Name, the number of patients tested (No. tested), and the percentage of patients in which expression was detected at greater than or equal to a two-fold increase (>2x) relative to matched normal control tissue versus cancerous tissue.

TABLE 2

SEQ ID NO:	Sequence Name	No. tested	>2x up 95% conf.
739	RTA00000181AF.p.12.3	33	48.48
1899	RTA00000345F.j.09.1	33	48.48
2007	RTA00000400F.g.08.1	28	46.43

[redacted]

17. The data above support the assertion that a polynucleotide having a sequence of SEQ ID NOS:739, 1899 or 2007 represents genes that are differentially expressed in cancer cells, thus supporting the assertion that the claimed invention has utility in detecting cancer cells. Specifically, detection of gene products that correspond to a genes having a sequence of SEQ ID NOS:739, 1899, and 2007 can provide an indicator that the cell is cancerous, and may provide a therapeutic and/or diagnostic target.

[redacted]

18. I, Filippo M. Randazzo, hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the United States Code, and that such will false statements may jeopardize the validity of the application or any patent issuing thereon.

5/25/01
Date

Filippo M. Randazzo

19. I, George M. Lamson, hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the United States Code, and that such will false statements may jeopardize the validity of the application or any patent issuing thereon.

5/25/01
Date

George F. Lamson

Attachments: Table 1 of patient data

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Attachment 1

TABLE 1

Patient ID	Path Report ID	Anatomical Loc	Primary Tumor Size	Primary Tumor Grade	Histopath Grade	Local Invasion	Lymphnode Met	Incidence Lymphnode Met	Regional Lymphnode Grade	Distant Met & Loc	Descrip Distant Met	Dist Met Grade	Comment
15	21	Ascending colon	4.0	T3	G2	Extending into subserosal adipose tissue	positive	3/8	N1	negative		MX	invasive adeno-carcinoma, moderately differentiated; focal perineural invasion is seen
52	71	Ascending colon	9.0	T3	G3	Invasion through muscularis propria, subserosal involvement; ileocec. valve involvement	negative	0/12	N0	negative		M0	Hyperplastic polyp in appendix
121	140	Sigmoid	6	T4	G2	Invasion of muscularis propria into serosa, involving submucosa of urinary bladder	negative	0/34	N0	negative		M0	Perineural invasion; donut anastomosis negative. One tubulovillous and one tubular adenoma with no high grade dysplasia.

Attachment 1

Patient ID	Path Report ID	Anatomical Loc	Primary Tumor Size	Primary Tumor Grade	Histopath Grade	Local Invasion	Lymphnode Met	Incidence Lymphnode Met	Regional Lymphnode Grade	Distant Met & Loc	Descrip Distant Met	Dist Met Grade	Comment
125	144	Cecum	6	T3	G2	Invasion through the muscularis propria into suserosal adipose tissue. Ileocecal junction.	negative	0/19	N0	negative		M0	patient history of metastatic melanoma
128	147	Transverse colon	5.0	T3	G2	Invasion of muscularis propria into percolonic fat	positive	1/5	N1	negative		M0	
130	149	Splenic flexure	5.5	T3		through wall and into surrounding adipose tissue	positive	10/24	N2	negative		M1	
133	152	Rectum	5.0	T3	G2	Invasion through muscularis propria into non-peritonealized pericolic tissue; gross configuration is annular.	negative	0/9	N0	negative		M0	Small separate tubular adenoma (0.4 cm)

Attachment 1

Patient ID	Path Report ID	Anatomical Loc	Primary Tumor Size	Primary Tumor Grade	Histopath Grade	Local Invasion	Lymphnode Met	Incidence Lymphnode Met	Regional Lymphnode Grade	Distant Met & Loc	Descrip Distant Met	Dist Met Grade	Comment
141	160	Cecum	5.5	T3	G2	Invasion of muscularis propria into pericolonic adipose tissue, but not through serosa. Arising from tubular adenoma.	positive	7/21	N2	positive (Liver)	adenocarcinoma consistant with primary	M1	Perineural invasion identified adjacent to metastatic adeno-carcinoma.
156	175	Hepatic flexure	3.8	T3	G2	Invasion through mucsularis propria into subserosa/pericolic adipose, no serosal involvement. Gross configuration annular.	positive	2/13	N1	negative		M0	Separate tubolovillous and tubular adenomas

Attachment 1

Patient ID	Path Report ID	Anatomical Loc	Primary Tumor Size	Primary Tumor Grade	Histopath Grade	Local Invasion	Lymphnode Met	Incidence Lymphnode Met	Regional Lymphnode Grade	Distant Met & Loc	Descrip Distant Met	Dist Met Grade	Comment
228	247	Rectum	5.8	T3	G2 to G3	Invasion through muscularis propria to involve subserosal, perirectoal adipose, and serosa	positive	1/8	N1	negative		MX	Hyperplastic polyps
264	283	Ascending colon	5.5	T3	G2	Invasion through muscularis propria into subserosal adipose tissue.	negative	0/10	N0	negative		M0	Tubulovillous adenoma with high grade dysplasia
266	285	Transverse colon	9	T3	G2	Invades through muscularis propria to involve pericolonic adipose, extends to serosa.	negative	0/15	N1	positive (Mesenteric deposit)	0.4 cm, may represent lymph node completely replaced by tumor	MX	

Attachment 1

Patient ID	Path Report ID	Anatomical Loc	Primary Tumor Size	Primary Tumor Grade	Histopath Grade	Local Invasion	Lymphnode Met	Incidence Lymphnode Met	Regional Lymphnode Grade	Distant Met & Loc	Descrip Distant Met	Dist Met Grade	Comment
268	287	Cecum	6.5	T2	G2	Invades full thickness of muscularis propria, but mesenteric adipose free of malignancy	negative	0/12	N0	negative		M0	
278	297	Rectum	4	T3	G2	Invasion into perirectal adipose tissue.	positive	7/10	N2	negative		M0	Descending colon polyps, no HGD or carcinoma identified.
295	314	Ascending colon	5.0	T3	G2	Invasion through muscularis propria into percolic adipose tissue.	negative	0/12	N0	negative		M0	Melanosis coli and diverticular disease.
339	358	Rectosigmoid	6	T3	G2	Extends into perirectal fat but does not reach serosa	negative	0/6	N0	negative		M0	1 hyperplastic polyp identified

Attachment 1

Patient ID	Path Report ID	Anatomical Loc	Primary Tumor Size	Primary Tumor Grade	Histopath Grade	Local Invasion	Lymphnode Met	Incidence Lymphnode Met	Regional Lymphnode Grade	Distant Met & Loc	Descrip Distant Met	Dist Met Grade	Comment
341	360	Ascending colon	2 cm invasive	T3	G2	Invasion through muscularis propria to involve pericolonic fat. Arising from villous adenoma.	negative	0/4	N0	negative		MX	
356	375	Sigmoid	6.5	T3	G2	Through colon wall into subserosal adipose tissue. No serosal spread seen.	negative	0/4	N0	negative		M0	
360	412	Ascending colon	4.3	T3	G2	Invasion thru muscularis propria to pericolonic fat	positive	1/5	N1	negative		M0	Two mucosal polyps
392	444	Ascending colon	2	T3	G2	Invasion through muscularis propria into subserosal adipose tissue, not serosa.	positive	1/6	N1	positive (Liver)	Macro-vesicular and micro-vesicular steatosis	M1	Tumor arising at prior ileocolic surgical anastomosis.

Attachment 1

Patient ID	Path Report ID	Anatomical Loc	Primary Tumor Size	Primary Tumor Grade	Histopath Grade	Local Invasion	Lymphnode Met	Incidence Lymphnode Met	Regional Lymphnode Grade	Distant Met & Loc	Descrip Distant Met	Dist Met Grade	Comment
393	445	Cecum	6.0	T3	G2	Cecum, invades through muscularis propria to involve subserosal adipose tissue but not serosa.	negative	0/21	N0	negative		M0	
413	465	Ascending colon	4.8	T3	G2	Invasive through muscularis to involve periserosal fat; abutting ileocecal junction.	negative	0/7	N0	positive (Liver)	adeno-carcinoma in multiple slides	M1	rediagnosis of oophorectomy path to metastatic colon cancer.
505	383		7.5 cm max dim	T3	G2	Invasion through muscularis propria involving pericolic adipose, serosal surface uninvolved	positive	2/17	N1	positive (Liver)	moderately differentiated adenocarcinoma, consis-tent with primary	M1	Anatomical location of primary not notated in report. Evidence of chronic colitis.

Attachment 1

Patient ID	Path Report ID	Anatomical Loc	Primary Tumor Size	Primary Tumor Grade	Histopath Grade	Local Invasion	Lymphnode Met	Incidence Lymphnode Met	Regional Lymphnode Grade	Distant Met & Loc	Descrip Distant Met	Dist Met Grade	Comment
517	395	Sigmoid	3	T3	G2	penetrates muscularis propria, involves pericolonic fat.	positive	6/6	N2	negative		M0	No mention of distant met in report
534	553	Ascending colon	12	T3	G3	Invasion through the muscularis propria involving pericolic fat. Serosa free of tumor.	negative	0/8	N0	negative		M0	Omentum with fibrosis and fat necrosis. Small bowel with acute and chronic serositis, focal abscess and adhesions.
546	565	Ascending colon	5.5	T3	G2	Invasion through muscularis propria extensively through submucosal and extending to serosa.	positive	6/12	N2	positive (Liver)	metastatic adenocarcinoma	M1	

Attachment 1

Patient ID	Path Report ID	Anatomical Loc	Primary Tumor Size	Primary Tumor Grade	Histopath Grade	Local Invasion	Lymphnode Met	Incidence Lymphnode Met	Regional Lymphnode Grade	Distant Met & Loc	Descrip Distant Met	Dist Met Grade	Comment
577	596	Cecum	11.5	T3	G2	Invasion through the bowel wall, into suberosal adipose. Serosal surface free of tumor.	negative	0/58	N0	negative		M0	Appendix dilated and fibrotic, but not involved by tumor
695	714	Cecum	14	T3	G2	extending through bowel wall into serosal fat	negative	0/22	N0	negative		MX	tubular adenoma and hyperplstic polyps present, moderately differentiated adenoma with mucinous diferentiation (% not stated)
784	803	Ascending colon	3.5	T3	G3	through muscularis propria into pericolic soft tissues	positive	5/17	N2	positive (Liver)		M1	invasive poorly differentiated adeno-squamous carcinoma

Attachment 1

Patient ID	Path Report ID	Anatomical Loc	Primary Tumor Size	Primary Tumor Grade	Histopath Grade	Local Invasion	Lymphnode Met	Incidence Lymphnode Met	Regional Lymphnode Grade	Distant Met & Loc	Descrip Distant Met	Dist Met Grade	Comment
786	805	Descending colon	9.5	T3	G2	through muscularis propria into pericolic fat, but not at serosal surface	negative	0/12	N0	positive (Liver)		M1	moderately differentiated invasive adenocarcinoma
791	810	Ascending colon	5.8	T3	G3	through the muscularis propria into pericolic fat	positive	13/25	N2	positive (Liver)		M1	poorly differentiated invasive colonic adeno-carcinoma
888	908	Ascending colon	2.0	T2	G1	into muscularis propria	positive	3/21	N0	positive (Liver)		M1	well- to moderately-differentiated adeno-carcinoma; this patient has tumors of the ascending colon and the sigmoid colon
889	909	Cecum	4.8	T3	G2	through muscularis propria int subserosal tissue	positive	1/4	N1	positive (Liver)		M1	moderately differentiated adeno-carcinoma

Atty Docket No. 2300-1481

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Typed or Printed Name	Steven F. Goldstein		
Signature	Steven F. Goldstein	**Date**	May 29, 2001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	
Williams, et al.	Group Art Unit: 1631
Serial No.: 09/297,648	Examiner: J. Brusca
Filing Date: March 10, 2000	
Title: *Novel Human Genes and Gene Expression Products II*	

DECLARATION OF CAROL L. FRANCIS UNDER 37 C.F.R. § 1.132

The Commissioner of
Patent and Trademarks
Washington, D.C. 20231

Sir:

I, Carol L. Francis, do hereby declare as follows:

I am an attorney in the law firm of Bozicevic, Field & Francis, LLP. My official place of business is located at 200 Middlefield Road, Suite 200, Menlo Park, California, 94025.

I represent the applicants of U.S. Patent Application Serial No. 09/297,648 before the U.S. Patent and Trademark Office.

The following cell lines were deposited with the American Type Culture Collection:

Cell Line	Deposit Date	ATCC Accession No.
KM12L4-A	March 19, 1998	CRL-12496
Km12C	May 15, 1998	CRL-12533
MDA-MB-231	May 15, 1998	CRL-12532
MCF-7	October 9, 1998	CRL-12584

The following cDNA libraries were deposited with the American Type Culture Collection:

cDNA Library	Deposit Date	ATCC Accession No.
ES17	January 22, 1999	207064
ES18	January 22, 1999	207065
ES19	January 22, 1999	207066
ES20	January 22, 1999	207067
ES21	January 22, 1999	207068
ES22	January 22, 1999	207069
ES23	January 22, 1999	207070
ES24	January 22, 1999	207071
ES25	January 22, 1999	207072
ES26	January 22, 1999	207073
ES27	January 22, 1999	207074
ES28	January 22, 1999	207075
ES29	January 22, 1999	207076
ES30	January 22, 1999	207077
ES31	January 22, 1999	207078
ES32	January 22, 1999	207079

cDNA Library	Deposit Date	ATCC Accession No.
ES33	January 22, 1999	207080

The above material has been deposited with the American Type Culture Collection, Rockville, Maryland, under the accession number indicated. These deposits will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. The deposit will be maintained for a period of at least 30 years following issuance of this patent, or for the enforceable life of the patent, whichever is greater. Upon the granting of a patent, all restrictions on the availability to the public of the deposited material will be irrevocably removed.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: May 29, 2001 By: Carol L. Francis

Carol L. Francis
Registration No. 36,513

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